REMARKS

CLAIM OBJECTION

On page 2, the Office objected to claim 57 since "plamid" should be "plasmid" in lines 7 and 13.

In response, applicants have made the required amendments.

FURTHER CLAIM AMENDMENTS

Applicants have amended claim 70 to replace the reference to a "pharmaceutical drug" with that to a "ligand of an orphan receptor." Support for this amendment can be found in paragraph [0261] to [0263], in particular paragraph [0263], of the publication of the present application (US Pat Pub. **20050106636**).

ANTICIPATION REJECTION

Applicants would like to thank the Office for withdrawing the anticipation rejections in view of applicants' argument set forth in applicants' after final response filed on January 19, 2010.

OBVIOUSNESS REJECTIONS

Starting on page 4, the Office rejected claims 48-55, 57-62 and 64-67 under 35 U.S.C. 103(a) as being unpatentable over Stagljar et al (PNAS 95:5187-5192, 1998, specifically pp. 5187, 5191 and figure 2; hereinafter "Stagljar") in view of US 2005/0277116 (McKeon et al.) and US 6,251,676 (Shioda et al.).

Stagljar is said to teach a split-ubiquitin system for detecting the interaction between two membrane bound proteins by introducing and coexpressing plasmids that encode the fusion proteins Ost-1 -Nub or Nub-Alg5 with Wbp1-Cub-PLV into S. *cerevisiae* strain yeast cells carrying lacZ and HIS3 reporter genes under the control of LexA-binding sites and testing cells for P-gal activity. The Ostl -Nub fusion protein is said to consist of a portion of Ostl p ER membrane protein and the Nub module. The Nub-Alg5 fusion protein is said to consist of the Alg5 ER membrane protein and the Nub module. The Wbp1-Cub-PLV protein is said to consist of a portion of the Wbp1 p ER transmembrane protein, the Cub module, and the PLV transcriptional activator (abstract, page 5187,right column, last paragraph to end of page 5189 and Figure 2).

The Office expressed the opinion that Stagljar meets all limitations of claims of the rejected claims, apart from the episomal maintenance of the bait and prey vector.

However, the Office referred to US 2005/0277116 (McKeon et al., hereinafter "McKeon"), in particular to paragraph 25, in which McKeon is said to teach that both the bait and prey vectors can be maintained episomally.
In addition, the Office relied on US 6,251,676 (Shioda et al., hereinafter "Shioda"), in particular its first column, for teaching a method for protein-protein interaction with bait and prey vectors, wherein the prey vector can be maintained episomally. Shioda is said to teach that a vector maintained episomally will not integrate and potentially damage the cell.

The Office expressed the opinion that the ordinary skilled artisan would have been motivated to combine the teachings of Stagjlar with the teachings of McKeon and Shioda because Shioda teaches that if a plasmid is maintained episomally in a closed circular form, the plasmid can be readily introduced and recovered from a bacterial host cell (*emphasis added*). Thus, the Office argues, it would have been obvious to one of ordinary skill in the art [to combine the references] because Shioda teaches that a vector maintained episomally will not integrate and potentially damage the cell (phrase in brackets added- the Office's argument appears otherwise incomplete). The Office concluded that, given these teachings that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Applicants have detailed in previous correspondence that while Stagljar teaches that his plasmid encoding an N-terminal part of split ubiquitin (e.g., "Nubl") can be maintained episomally, Stagljar does NOT teach that the plasmid encoding the membrane protein of interest, as well as "Cub" and, in particular also, a transcriptional activator and thus the plasmid disclosed in Stagljar containing elements of the claimed "bait vector" of the present invention, namely pRS305 (Δwbp1-Cub-PLV), is maintained episomally. Rather this plasmid is integrated into the endogene wbp1 gene of the yeast host cell. Thus, in Stagljar's integrated set up there is only one wbp1 gene in the cells, namely the integrated one, and all Wbp1 protein within the cell will be tagged with Cub-PLV.

As explained in the accompanying declaration by Igor Stagljar, episomal expression of Stagljar's pRS305 (Δwbp1-Cub-PLV) on the other hand would be expected to lead to two

types of Wbp1 protein in the cell, one that is tagged with Cub-PLV (the episomally maintained one) and one Wbp1 that is not tagged (the chromosomal one). This un-tagged Wbp1 protein could be expected to compete with the episomally expressed Cub-PLV tagged Wbp1 protein for protein interactions and thus to substantially compromise the sensitivity of Stagljar's assay.

Applicants note that Stagljar states that the intended purpose of his research is the analysis of interactions between membrane proteins. The modification that the Office suggests, namely the episomal maintenance of the bait vector, would provide not only a tagged Wbp1 protein but also untagged Wbp1 protein, which could be expected to interfere with Stagljar's analysis of interactions between membrane proteins. Thus, the modification that the Office proposes does render Stagljar unsatisfactory for its intended purpose. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). As a result, there is no suggestion or motivation to make the proposed modification (MPEP §2143.01).

Also, as noted above, the Office expressed the opinion that the ordinary skilled artisan would have been motivated to combine the teachings of Stagjlar, with the teachings of McKeon and Shioda because Shioda teaches that if a plasmid is maintained episomally in a closed circular form, the plasmid can be readily introduced and recovered from a bacterial host cell (*emphasis added*).
Applicants note that Shioda teaches that its plasmid can be readily recovered from a mammalian host cell, not a bacterial host cell.
Indeed, Shioda transfects its prey plasmid containing the ori-P (the Epstein Barr virus of replication) into a mammalian cell that expresses Epstein Barr nuclear antigen-1 (EBNA-1) (Shioda, col. 1, lines 43-47; col.4, lines 40 to 43). The ori-P is responsible for the features the Office refers to as making the combination with Stagljar desirable, namely the ability of the plasmid to "replicate episomally and indefinitely without damaging the mammalian cell or integrating into the genomic DNA." (abstract).
In column 7, lines 46 to 60, Shioda describes which origins of replication are desirable for obtain these features. As the only example, Shioda refers to ori-P, which is said to "replicate stably in a mammalian cell that expresses EBNA-1".

Applicants note that Stagljar works with yeast cells rather than mammalian cells. These yeast cells do not express EBNA-1 to ensure a stable replication of a vector containing ori-P or an

equivalent that would interact with another appropriate origin of replication.
The Office has not clarified how the specific teachings of Shioda's system can be readily applied to the teachings of Stagljar's yeast system. Applicants note that McKeon, also describing a mammalian system, does not resolve the issue. Accordingly, applicants respectfully submit that no *prima facie* case of obviousness has been established.

In addition, the Office refers to McKeon for the disclosure of a system in which both the bait and the prey vector are expressed episomally. The Office relies on Shioda for the advantages obtained from such an episomal expression, especially the advantages mentioned in the context of Shioda's prey vector.
Applicants note that Shioda describes his bait protein/ bait vector in columns 5 and 6. Applicants further note that in column 6, lines 45 to 46, Shioda states with regard to the bait vector that "[p]referably, the vector is integrated into a chromosome of the cell."
Thus, assuming the person skilled in the art, would after reviewing McKeon come to the conclusion that an episomally maintained bait and prey vector would be a possibility, what applicants deny, this person would in the process of reading Shioda and, according to the Office's analysis, obtaining the motivation to combine the references, be taken aback by the notion that Shioda considers integration of the bait vector a preferred embodiment.
Applicants submit that the Office has not explained how the person skilled in the art would resolve this conflict. Accordingly, applicants submit that the Office has not established a *prima facie* case of obviousness.

Starting on page 10, the Office rejected claims 71 to 73 and 78 to 81 under 35 USC §103(a) as being unpatentable over Stagljar, McKeon and Shioda in view of Clarke et al. (hereinafter Clark).

Applicants note that the Office acknowledged that Stagljar teaches the CEN/ARS origin of replication only in context of the prey vector NubI-ALG5, but not in the context of a bait vector. The Office also acknowledged that McKeon and Shioda do not teach a CEN/ARS origin of replication.

However, the Office referred to Clarke (Ann. Rev. Genet. 19: 29-56, esp. pp- 32-33 (1985)) for use of the CEN/ARS vector as a low copy vector. The Office cited as motivation to combine the teachings of Stagljar, McKeon and Shioda and Clarke, Clarke's teaching that

the copy number of the *CEN/ARS* vector is only 1-2 copies per cell and a CEN/ARS vector greatly increases mitotic stability.

Clarke indeed teaches that the addition of a *CEN* sequence to circular *ARS* plasmids in S. *cerevisiae* increases the mitotic stability relative to a circular *ARS* plasmid not containing the *CEN* sequence. However, Clarke notes in the same paragraph on page 32 that "[n]evertheless, *CEN ARS* plasmids are two to three orders of magnitude less stable than normal yeast chromosomes."

Thus, applicants submit that while Clarke recommends a *CEN ARS* plasmid over an *ARS* plasmid to obtain mitotic stability, the above cited passage of Clarke indicates that an integration into the yeast chromosome as disclosed by Stagljar would increase the mitotic stability even more, namely two or three orders of magnitude.

Thus, applicants respectfully submit that there is nothing in Clarke that suggests that the mitotic stability of a plasmid containing CEN/ARS origin of replication exceeds that of an intergrated structure or even of the ori-P as disclosed Shioda.

Accordingly, applicants respectfully submit that the Office did not establish a *prima facie* case of obviousness with respect to 71 to 73 and 78 to 81.

Starting on page 5, the Office rejected claims 68 and 70 as unpatentable over Staggljar, McKeon and Shioda as applied to claims 48 to 55, 57 to 62 and 64 to 67 above, and further in view of Ehrhard et al. (Nature Biotech. 18: 1075-1079, 2000; hereinafter "Ehrhard").

The Office acknowledged that Stagljar and Shioda, while being said to disclose all the limitations of the claims, do not teach identifying a pharmaceutical drug.

The Office argued Stagljar, McKeon and Shioda as applied to claims 48 to 55, 57 to 62 and 64 to 67 above, but did not teach identifying pharmaceutical drugs for their ability to interfere with protein-protein interactions. Ehrhard is said to teach a method of identifying compounds for their ability to interfere with protein-protein interactions.

Applicants have set forth above the reasons why Stagljar, McKeon and Shioda do not render obvious claims 48 to 55, 57 to 62 and 64 to 67.

Ehrhard's method relies on G-protein fusions to monitor integral membrane protein-protein interactions. The Office has not provided any reasoning how Ehrhard addresses the deficiencies of Stagljar , McKeon and Shioda detailed above. Accordingly, no *prima facie* case of obviousness has been established by the Office (MPEP §2142, MPEP §2143). Applicants submit that Ehrhard does not make obvious these deficiencies of Stagljar, McKeon and Shioda.

Applicants would also like to draw the Office attention to the amendments to claim 70.

Starting on page 7, the Office rejected claim 56 under 35 U.S.C. 103(a) as being unpatentable over Stagljar, McKeon and Shioda as applied to claims 48 to 55, 57 to 62 and 64 to 67 above, and further in view of Wedegaertner et al (J. Biochem. 270(2): 503-506, 1995, esp. 503, hereinafter "Wedegaertner") and Friedberg et al. (Biochem J. 303: 967-972, 1994, hereinafter "Friedberg").

Applicants have set forth above the reasons why Stagljar, McKeon and Shioda do not render obvious claims 48 to 55, 57 to 62 and 64 to 67.
The Office has not provided any reasoning how Wedegaertner and Friedberg address the deficiencies of Stagljar, McKeon and Shioda detailed above. Accordingly, no *prima facie* case of obviousness has been established by the Office (MPEP §2142, MPEP §2143). Applicants submit that Wedegaertner and Friedberg do not make obvious these deficiencies of Stagljar, McKeon and Shioda.

Starting on page 8, the Office rejected claims 63, 75 and 76 under 35 U.S.C. 103(a) as being unpatentable over Stagljar, McKeon and Shioda as applied to claims 48-55, 57-62, 64-67 above, and further in view of Mumberg et al. (Gene 156:119-122, 1995, hereinafter "Mumberg").

The Office has not provided any reasoning how Mumberg addresses the deficiencies of Stagljar, McKeon and Shioda detailed above. Accordingly, no *prima facie* case of obviousness has been established by the Office (MPEP §2142, MPEP §2143). Applicants submit that Mumberg does not make obvious these deficiencies of Stagljar, McKeon and Shioda.

Starting on page 9, the Office rejected claims 63, 75 and 77 under 35 U.S.C. 103(a) as being unpatentable over Stagljar et al, US 2005/0277116 and US 6,251,676 as applied to claims 48-55, 57-62, 64-67 above, and further in view of Ecker et al. (J. Biochem. 262(8): 3524-2527, 1987, especially p. 3524-3525).

The Office has not provided any reasoning how Ecker addresses the deficiencies of Stagljar, McKeon and Shioda detailed above. Accordingly, no *prima facie* case of obviousness has been established by the Office (MPEP §2142, MPEP §2143). Applicants submit that Ecker does not make obvious these deficiencies of Stagljar, McKeon and Shioda.

Applicants submit that the above demonstrates that the rejected claims are patentable over the art cited. Accordingly, an early issuance of a notice of allowance is respectfully requested. In case there should be any further issues to address, the undersigned urges the Office to call her at directly at **(301) 657-1282** to resolve these issues expeditiously.

The Commissioner is authorized to charge any fee deficiencies or overpayments to undersign's deposit account 50-3135.

Respectfully submitted,

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